

201-14046

October 13, 2005

Stephen Johnson, Administrator
US Environmental Protection Agency
Ariel Rios Building
Room 3000, #1101-A
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Subject: Comments on the HPV test plan for Ethylene Carbonate

Dear Administrator Johnson:

The following comments on the Huntsman Petrochemical Corporation (HPC) test plan for Ethylene Carbonate are submitted on behalf of the Physicians Committee for Responsible Medicine, People for the Ethical Treatment of Animals, the Humane Society of the United States, the Doris Day Animal League, and Earth Island Institute. These health, animal protection, and environmental organizations have a combined membership of more than ten million Americans.

HPC submitted its test plan on March 18, 2005, for Ethylene Carbonate (EC). EC has various well-characterized uses in the chemical industry. HPC does not propose any testing for the chemical, but uses a metabolite of EC, ethylene glycol (EG), to fulfill endpoints that are not addressed by tests using the chemical itself. These include acute toxicity to fish and daphnia, *in vivo* mammalian genetic toxicity, and reproductive mammalian toxicity.

We appreciate HPC's efforts to conduct thoughtful toxicology in order to avoid any animal testing. However, there are several ways in which the test plan submission could be strengthened. First, it is unclear from the test plan under what conditions this hydrolysis occurs. This should be established to support the appropriateness of the metabolite data on EG for the aquatic toxicity of EC. Additionally, data from both chemicals, which are available for daphnia, should be compared to support the use of EG data for the other aquatic toxicity endpoints.

This strategy should also be employed to support the use of EG to characterize the mammalian toxicity of EC. While general comparisons in the text allude to nephrotoxicity as a shared endpoint between the two chemicals, often a clearly-constructed table that compares the available data for both chemicals can increase a confidence in the bridging of data. In this case, it is possible to make such comparisons for both chemicals for acute toxicity, chronic toxicity, *in vitro* genetic toxicity, acute dermal toxicity, and developmental toxicity endpoints, since information on these endpoints is available on TOXNET.

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Although there is a concern regarding the formation of formate (formic acid) during the metabolic hydrolysis reaction *in vivo*, we consider this concern to be academic only. While the cited Hanley et al. (1989) reference does not specifically mention the proposed reaction, it is established in the literature that the enzymatic hydrolysis of EC forms EG and CO₂ (Yang et al., 1998). In this paper, the authors state that "The reaction would be expected to take the form of protonation of the carbonyl group of the carbonate, thereby providing a strong electrophilic center for the addition of water. Upon such addition, ring opening would be followed by elimination of CO₂." While the test plan summary does not detail the Hanley et al. (1989) metabolism study, the authors report that 60 percent of the EC dose was recovered as CO₂ in expired air.

Further proof, if needed, could be obtained by an *in vitro* enzymatic hydrolysis study. Though the Healy et al. (1989) study did not find hydrolysis of EC *in vitro*, the Yang et al. (1998) paper does identify the enzyme responsible for this reaction in rodents—a non-specific imidase.

Finally, if there is truly a concern that formate is formed from this reaction, this could simply be noted in the text as a possibility, along with appropriate human toxicity information available for formate.

Once referencing and analog chemical support issues are resolved, the test plan should be adequate for HPV program purposes. HPC has conducted a thoughtful analysis of the data. We offer these additional suggestions to strengthen the test plan and further support the approach offered. We concur that no additional animal tests should be conducted. This approach is consistent with the EPA's stated goal of maximizing the use of existing data in order to limit additional animal testing and to avoid a mere box-checking approach to toxicology.

Thank you for your attention to these comments. We may be reached at 202-686-2210, ext. 335, or via email at kstoick@pcrm.org.

Sincerely,

Kristie M Stoick, M.P.H.
Research Analyst

Chad B. Sandusky, Ph.D.
Director of Research

References

- Yang Y, SG Ramaswamy, WB Jakoby. 1998. Enzymatic hydrolysis of organic cyclic carbonates. *J Biol Chem* 273(14):7814-17.
- Hanley TR Jr, AM Schumann, PW Langvardt, TF Rusek, PG Watanabe. 1989. Metabolism and disposition of ethylene carbonate in Male Fischer 344 Rats. *Tox Appl Pharm* 100(1):24-31.